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IN THIS ISSUE

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IN BRIEF

Risk of Pulmonary Thromboembolism and Death with Tofacitinib *(Xeljanz)*

The FDA has required updates to the labeling of the Janus kinase (JAK) inhibitor tofacitinib *(Xeljanz, Xeljanz XR)* based on interim results of a postmarketing safety trial that showed an increased risk of pulmonary thromboembolism and death with a dosage of 10 mg twice daily.[1] Tofacitinib is approved for treatment of rheumatoid arthritis (RA),[2] psoriatic arthritis, and ulcerative colitis.

In the postmarketing trial, RA patients ≥50 years old taking methotrexate who had at least one cardiovascular risk factor were randomized to receive add-on treatment with tofacitinib 5 mg twice daily (the FDA-approved dosage for RA and psoriatic arthritis), tofacitinib 10 mg twice daily (an approved dosage for ulcerative colitis), or a tumor necrosis factor (TNF) inhibitor. At the time of the interim analysis in January 2019 (~3900 patient-years of data in each group), pulmonary thromboembolism had occurred in 19 patients taking tofacitinib 10 mg twice daily and in 3 patients taking a TNF inhibitor; 45 patients taking tofacitinib 10 mg twice daily and 25 taking a TNF inhibitor had died. Interim data from the 5-mg twice daily group have not been made available by the FDA. After the interim analysis, patients taking the higher dose of tofacitinib were transitioned into the 5 mg twice daily group; the trial is ongoing.[3]

Serious, sometimes fatal thromboembolic adverse events have also occurred with use of baricitinib *(Olumiant)*,[4] another JAK inhibitor that is FDA-approved for treatment of RA. Whether an increased risk of thromboembolism is a class effect of JAK inhibitors remains to be determined; RA itself has been associated with an increased thromboembolic risk.[5]

The tofacitinib package insert now contains a boxed warning describing the increased risk of thrombosis and mortality with a dosage of 10 mg twice daily and emphasizes that this dosage or *Xeljanz XR* 22 mg once daily is not recommended for treatment of RA or psoriatic arthritis. For treatment of ulcerative colitis, tofacitinib is now only indicated in patients who have had an inadequate response or intolerance to TNF inhibitors; for these patients, the 10-mg twice daily dosage is still recommended as induction therapy for 8 weeks (can be continued for up to 16 weeks) and for maintenance treatment when there is loss of response to a dosage of 5 mg twice daily. ■

1. FDA drug safety communication: FDA approves boxed warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR). July 26, 2019. Available at: www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and. Accessed August 15, 2019.
2. Tofacitinib for rheumatoid arthritis. Med Lett Drugs Ther 2013; 55:1.
3. FDA drug safety communication: Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate. February 25, 2019. Available at: https://www.fda.gov/media/120485/download. Accessed August 15, 2019.
4. Baricitinib (Olumiant) for rheumatoid arthritis. Med Lett Drugs Ther 2018; 60:120.
5. IC Scott et al. Thromboembolism with Janus kinase (JAK) inhibitors for rheumatoid arthritis: how real is the risk? Drug Saf 2018; 41:645.

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